contd. a3

13. A method of treating inflammation in warm-blooded animals comprising administering to warm-blooded animals in need thereof an anti-inflammatorily effective amount of a compound of claim 1.--

REMARKS

The amendment is presented to insert reference to the PCT application, remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

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CAM:sd
Enclosures: Marked-up Version of Specification and Claims
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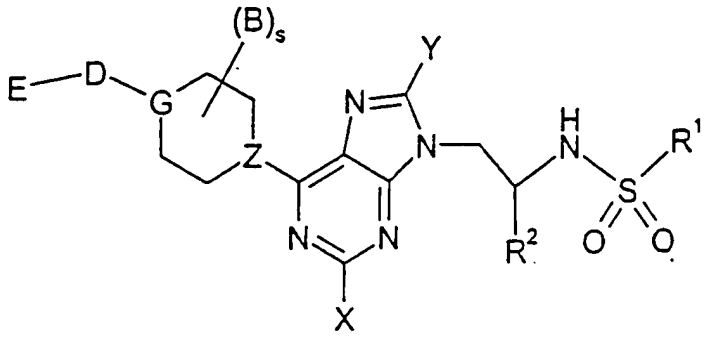
Substituted purine derivatives as inhibitors of cell adhesion

--This application is a 371 of PCT/EP00/05921 filed June 26, 2000.--

The present invention relates to compounds of the formula I,



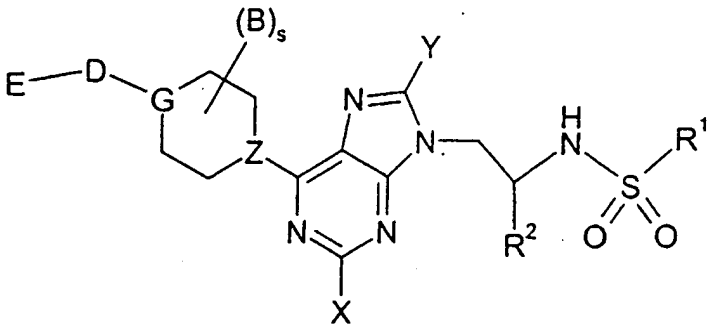
I

in which B, D, E, G, X, Y, Z, R^1, R^2 and s have the meanings indicated below, their physiologically tolerable salts and their prodrugs. The compounds of the formula I are valuable pharmacologically active compounds. They are vitronectin receptor antagonists and inhibitors of cell adhesion and are suitable for the therapy and prophylaxis of illnesses which are based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. For example, they can be applied for inhibiting bone resorption by osteoclasts and thus for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth musculature. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.

Human bones are subject to a constant dynamic renovation process comprising bone resorption and bone formation. These processes are controlled by types of cell specialized for these purposes. Bone resorption is based on the destruction of bone matrix by osteoclasts. The majority of bone disorders are based on a disturbed equilibrium between bone formation and bone resorption. Osteoporosis is a disease

Patent claims

1. A compound of the formula I



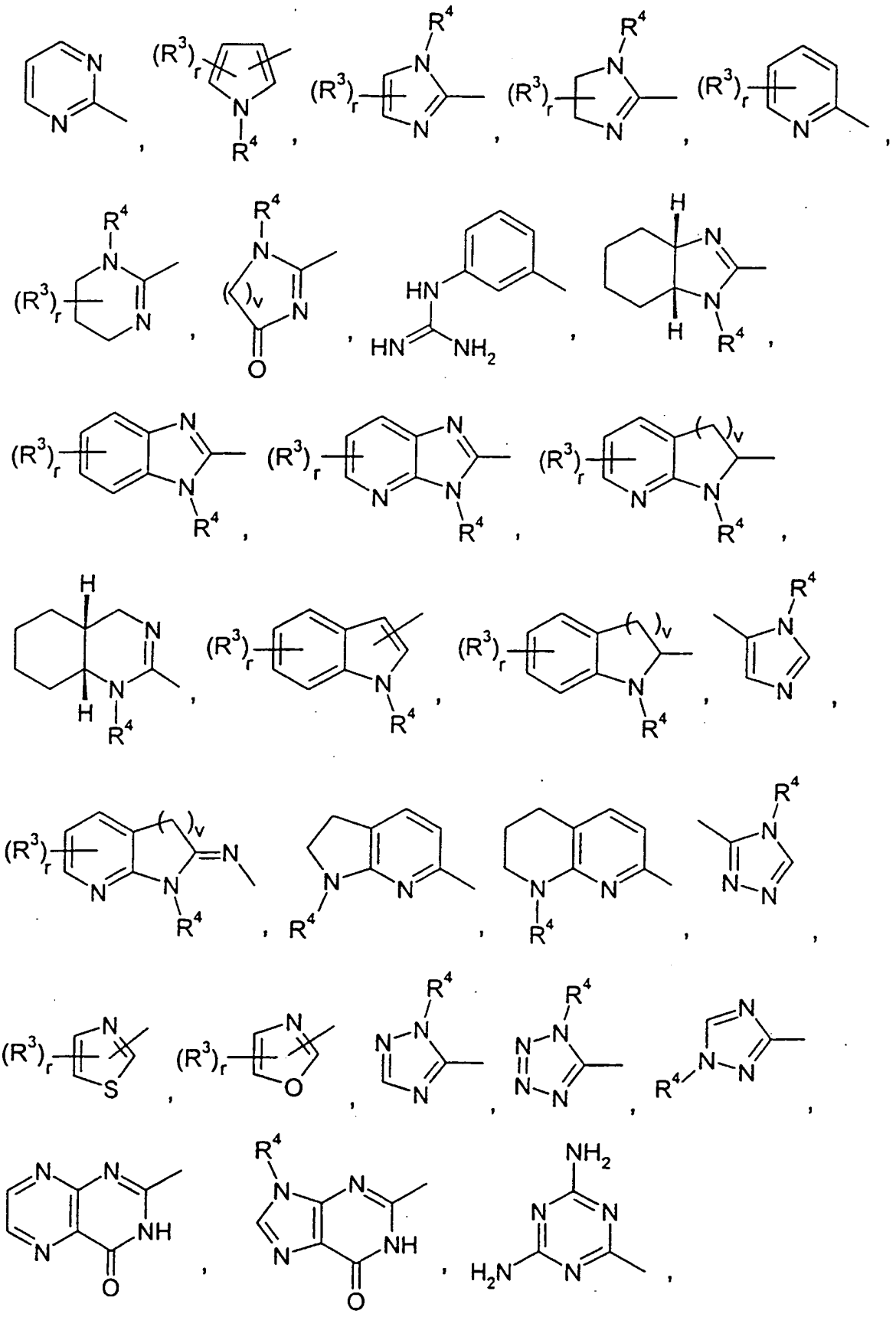
I

wherein

B is (C_1-C_{18})-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl, (C_5-C_{14})-aryl-(C_1-C_8)-alkyl-, (C_5-C_{14})-heteroaryl, (C_5-C_{14})-heteroaryl-(C_1-C_8)-alkyl-, fluorine, chlorine, bromine, hydroxy, cyano, trifluoromethyl, nitro, hydroxycarbonyl-, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl-, (C_1-C_6)-alkoxycarbonyl-, (C_1-C_6)-alkylcarbonyl-, (C_5-C_{14})-arylcarbonyl-, (C_1-C_6)-alkylaminocarbonyl-, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylcarbonyl-, (C_1-C_6)-alkanoylamino-, (C_1-C_6)-alkylsulfonylamino-, (C_5-C_{14})-arylsulfonylamino-, (C_1-C_6)-alkylamino-, di-$((C_1-C_6)$-alkyl)amino-, (C_1-C_6)-alkylsulfonyl-, aminosulfonyl-, (C_5-C_{14})-arylsulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylsulfonyl-, (C_5-C_{14})-aryl ~~or~~ and (C_5-C_{14})-heteroaryl, where all residues B are independent of one another ~~and can be identical or different~~, or B denotes an aromatic or non-aromatic ring system ~~that is~~ fused to the 6-membered ring containing the groups G and Z;

D is -C(O)-N(R^6)-, -NR^6-C(O)-, -NR^6-C(O)-N(R^6)-, -NR^6-C(S)-N(R^6)-, -C(S)-N(R^6)- or -C(R^6)=N-N(R^6)-, where the divalent ~~residues representing~~ D are bonded to ~~the group~~ E via the free bond on their right side;

E is ~~a residue from the series consisting of~~



r is zero, one, two, three or four;

s is zero, one, two, three or four;

v is one, two or three; and

p is one or two;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their non-toxic physiologically tolerable salts ~~and their prodrugs~~; and

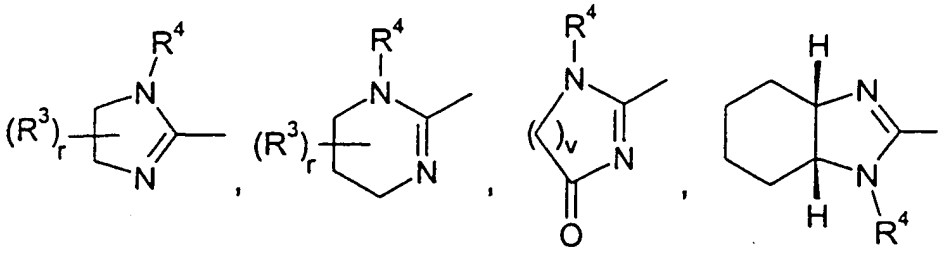
where, instead of the purine structure shown in formula I, also a 3-deazapurine structure, a 7-deazapurine structure or a 7-deaza-8-azapurine structure ~~can be~~ is present.

2. A compound of ~~the formula I as claimed in~~ claim 1, wherein

B is (C_1-C_{18})-alkyl or hydroxy, ~~where~~ and all ~~residues~~ B are independent of one another ~~and can be identical or different~~;

D is -C(O)-N(R^6)-, ~~where this divalent residue is~~ bonded to the group E via its nitrogen atom;

E is ~~a residue~~ selected from the ~~series~~ group consisting of



and $R^6R^{6'}N$-C(=NR^6)-;

G is N or CH;

X is hydrogen;

one, two or three ring carbon atoms can be replaced by heteroatoms from the series consisting of nitrogen, oxygen and sulfur,

or R^6 and $R^{6'}$ together with the nitrogen atom to which they are bonded form a 4-membered to 6-membered ring system which in addition to the nitrogen atom to which R^6 and $R^{6'}$ are bonded can contain one, two or three ring heteroatoms from the series consisting of nitrogen, oxygen and sulfur and which can be unsaturated or saturated,

where all residues R^6 and $R^{6'}$ are independent of one another ~~and can be identical or different;~~

r is zero, one, two, three or four;

s is zero, one, two, three or four;

v is one, two or three;

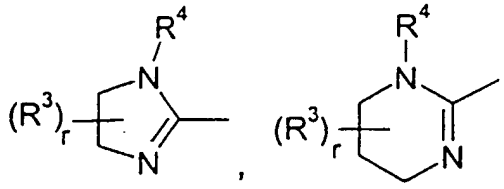
in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts ~~and their prodrugs~~.

3. A compound of ~~the formula I as claimed in~~ claims 1 ~~and/or 2~~, wherein

B is (C_1-C_6)-alkyl or hydroxy, where all ~~residues~~ B are independent of one another ~~and can be identical or different;~~

D is -C(O)-N(R^6)-, ~~where this divalent residue is~~ bonded to the group E via its nitrogen atom;

E is ~~a residue~~ from the ~~series~~ consisting of



and $R^6R^{6'}N$-C(=NR^6)-;

R^6 and $R^{6'}$ are hydrogen, (C_1-C_6)-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, or (C_5-C_{14})-aryl-(C_1-C_8)-alkyl-, or R^6 and $R^{6'}$ together with the nitrogen atom to which they are bonded form a 4-membered to 6-membered ring system which in addition to the nitrogen atom to which R^6 and $R^{6'}$ are bonded can contain one or two ring heteroatoms from the group consisting of nitrogen, oxygen and sulfur and which can be unsaturated or saturated,

where all R^6 and $R^{6'}$ are independent of one another

r is zero, one, two, three or four;

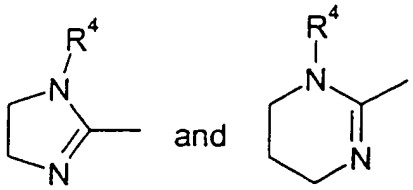
s is zero, one or two;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts.

4. A compound of claims 1 to 3, wherein

D is -C(O)-N(R^6)-, bonded to E via its nitrogen atom;

E is selected from the group consisting of



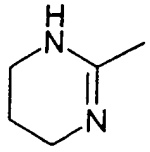
;

G is CH;

X is hydrogen;

Y is hydrogen;

E is ~~the residue~~



;

G is CH;

X is hydrogen;

Y is hydrogen;

Z is N;

R^1 is (A) $(C_1\text{-}C_{18})$-alkyl, $(C_3\text{-}C_{14})$-cycloalkyl, $(C_3\text{-}C_{14})$-cycloalkyl-$(C_1\text{-}C_8)$-alkyl-, $(C_5\text{-}C_{14})$-aryl, $(C_5\text{-}C_{14})$-aryl-$(C_1\text{-}C_8)$-alkyl-, $(C_5\text{-}C_{14})$-heteroaryl and $(C_5\text{-}C_{14})$-heteroaryl-$(C_1\text{-}C_8)$-alkyl- where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by ~~identical or different substituents from the series~~ at least one member of the group consisting of fluorine, chlorine, bromine, cyano, trifluoromethyl, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkoxy and $(C_5\text{-}C_{14})$-aryl;

R^2 is $-C(O)R^5$;

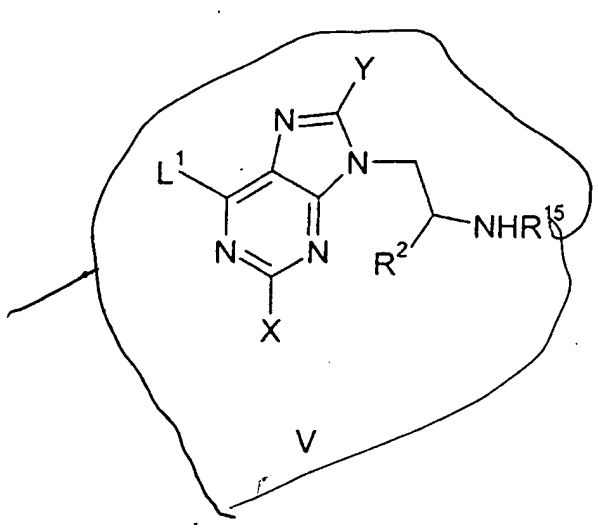
R^5 is hydroxy or $(C_1\text{-}C_6)$-alkoxy;

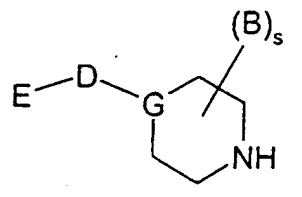
s is zero;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their non-toxic physiologically tolerable salts ~~and their prodrugs~~.

6. A process for the preparation of a compound ~~as claimed in one or more~~ of claims 1 ~~to 5~~, comprising reacting a compound of the formula V_1 with a compound of the

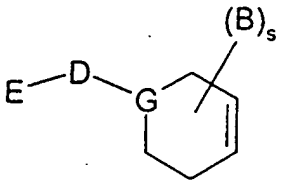
formula VIa or with a compound of the formula VIb





VIa

and



VIb

wherein L^1 is a leaving group, R^{15} is R^1-SO_2- or an amino protecting group and B, D, E, G, X, R^2 and s are defined as in claims 1 to ~~5~~ but where functional groups can also be present in the form of precursor groups or in protected form.

7. A pharmaceutical composition, comprising ~~at least one~~ a compound of ~~the formula I as claimed in one or more of~~ claims 1 ~~to 5, and/or its physiologically tolerable salts and/or its prodrugs~~ and a pharmaceutically acceptable carrier.

8. A compound of the formula I as claimed in one or more of claims 1 to 5 and/or its physiologically tolerable salts and/or its prodrugs for use as a pharmaceutical.

9. A compound of the formula I as claimed in one or more of claims 1 to 5 and/or its physiologically tolerable salts and/or its prodrugs for use as a vitronectin receptor antagonist.

10. A compound of the formula I as claimed in one or more of claims 1 to 5 and/or its physiologically tolerable salts and/or its prodrugs for use as an inhibitor of bone resorption, for the therapy or prophylaxis of osteoporosis, as an inhibitor of tumor growth or tumor metastasis, as an antiinflammatory, or for the therapy or prophylaxis of cardiovascular disorders, restenoses, arteriosclerosis, nephropathies,

R^6-C(=NR^6)-NR^6- and $R^6R^{6'}$N-C(=NR^6)-;

G is N, CH or C($(C_1$-$C_4)$-alkyl);

X is hydrogen, -$NR^6R^{6'}$, fluorine, chlorine, bromine, -OR^6, -SR^6, hydroxy-$(C_1$-$C_6)$-alkyl-NH-, (hydroxy-$(C_1$-$C_6)$-alkyl)$_2$N-, amino-$(C_1$-$C_6)$-alkyl-NH-, (amino-$(C_1$-$C_6)$-alkyl)$_2$N-, hydroxy-$(C_1$-$C_6)$-alkyl-O-, hydroxy-$(C_1$-$C_6)$-alkyl-S- or -NH-C(O)-R^6;

Y ~~has one of the meanings of~~ R^6, ~~or is~~ fluorine, chlorine, bromine, cyano, -$NR^6R^{6'}$, -OR^6, -SR^6 or hydroxy-$(C_1$-$C_6)$-alkyl-NH-;

Z is N or CH;

R^1 is $(C_1$-$C_{18})$-alkyl, $(C_3$-$C_{14})$-cycloalkyl, $(C_3$-$C_{14})$-cycloalkyl-$(C_1$-$C_8)$-alkyl-, $(C_5$-$C_{14})$-aryl, $(C_5$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkyl-, $(C_5$-$C_{14})$-heteroaryl or $(C_5$-$C_{14})$-heteroaryl-$(C_1$-$C_8)$-alkyl- where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by ~~identical or different substituents from the series~~ at least one member of the group consisting of fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, hydroxycarbonyl-, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, $(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkyl-, $(C_1$-$C_6)$-alkoxycarbonyl-, $(C_1$-$C_6)$-alkylcarbonyl-, $(C_1$-$C_6)$-alkylaminocarbonyl-, $(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkoxy-, $(C_5$-$C_{14})$-arylcarbonyl-, $(C_5$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkylcarbonyl-, $(C_1$-$C_6)$-alkanoylamino-, $(C_5$-$C_{14})$-arylsulfonylamino-, $(C_1$-$C_6)$-alkylsulfonylamino-, $(C_1$-$C_6)$-alkylamino-, di-$((C_1$-$C_6)$-alkyl)amino-, $(C_1$-$C_6)$-alkylsulfonyl-, $(C_1$-$C_6)$-alkylaminosulfonyl-, $(C_5$-$C_{14})$-arylaminosulfonyl-, $(C_5$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkylaminosulfonyl-, $(C_5$-$C_{14})$-arylsulfonyl-, $(C_5$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkylsulfonyl-, $(C_5$-$C_{14})$-aryl and $(C_5$-$C_{14})$-heteroaryl;

R^2 is -C(O)R^5, -C(S)R^5, -S(O)$_p$$R^5$, -P(O)$R^5R^{5'}$ ~~or a residue of~~ and a 4-membered to 8-membered saturated or unsaturated heterocycle which contains 1, 2, 3 or 4 heteroatoms selected from the ~~series~~ group consisting of nitrogen, oxygen and sulfur;

R^3 is $(C_1$-$C_{18})$-alkyl, $(C_3$-$C_{14})$-cycloalkyl, $(C_3$-$C_{14})$-cycloalkyl-$(C_1$-$C_8)$-alkyl-, $(C_5$-$C_{14})$-aryl, $(C_5$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkyl-, $(C_5$-$C_{14})$-heteroaryl, $(C_5$-$C_{14})$-heteroaryl-$(C_1$-$C_8)$-

alkyl-, fluorine, chlorine, bromine, hydroxy, cyano, trifluoromethyl, nitro, hydroxycarbonyl-, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl-, (C_1-C_6)-alkoxycarbonyl-, (C_1-C_6)-alkylcarbonyl-, (C_5-C_{14})-arylcarbonyl-, (C_1-C_6)-alkylaminocarbonyl-, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylcarbonyl-, (C_1-C_6)-alkanoylamino-, (C_1-C_6)-alkylsulfonylamino-, (C_5-C_{14})-arylsulfonylamino-, (C_1-C_6)-alkylamino-, di-$((C_1-C_6)$-alkyl$)$amino-, (C_1-C_6)-alkylsulfonyl-, aminosulfonyl-, (C_5-C_{14})-arylsulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylsulfonyl-, (C_5-C_{14})-aryl or (C_5-C_{14})-heteroaryl, where all residues R^3 are independent of one another and can be identical or different;

R^4 is hydrogen, (C_1-C_{10})-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl or (C_5-C_{14})-aryl-(C_1-C_8)-alkyl-;

R^5 and $R^{5'}$ are hydroxy, (C_1-C_8)-alkoxy, (C_5-C_{14})-aryl-(C_1-C_8)-alkoxy-, (C_1-C_8)-alkylcarbonyloxy-(C_1-C_4)-alkoxy-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylcarbonyloxy-(C_1-C_8)-alkoxy- or $-NR^6R^{6'}$, where the residues R^5 and $R^{5'}$ are independent of one another and can be identical or different;

R^6 and $R^{6'}$ are hydrogen, (C_1-C_{18})-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl where in the aryl residue one, two, three, four or five ring carbon atoms can be replaced by heteroatoms from the series consisting of nitrogen, oxygen and sulfur, or (C_5-C_{14})-aryl-(C_1-C_8)-alkyl- where in the aryl moiety of the aryl-alkyl- residue one, two, three, four or five ring carbon atoms can be replaced by heteroatoms from the series consisting of nitrogen, oxygen and sulfur,

or R^6 and $R^{6'}$ together with the nitrogen atom to which they are bonded form a 4-membered to 8-membered ring system which in addition to the nitrogen atom to which R^6 and $R^{6'}$ are bonded can contain one, two or three ring heteroatoms from the series consisting of nitrogen, oxygen and sulfur and which can be unsaturated or saturated,

where all residues R^6 and $R^{6'}$ are independent of one another and can be identical or different;

Y is hydrogen;

Z is N or CH;

R^1 is (A) (C_1-C_{18})-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl, (C_5-C_{14})-aryl-(C_1-C_8)-alkyl-, (C_5-C_{14})-heteroaryl and (C_5-C_{14})-heteroaryl-(C_1-C_8)-alkyl- where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by ~~identical or different substituents~~ at least one member selected from the ~~series~~ group consisting of fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, hydroxycarbonyl-, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl-, (C_1-C_6)-alkoxycarbonyl-, (C_1-C_6)-alkylcarbonyl-, (C_1-C_6)-alkylaminocarbonyl-, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy-, (C_5-C_{14})-arylcarbonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylcarbonyl-, (C_1-C_6)-alkanoylamino-, (C_5-C_{14})-arylsulfonylamino-, (C_1-C_6)-alkylsulfonylamino-, (C_1-C_6)-alkylamino-, di-$((C_1-C_6)$-alkyl)amino-, (C_1-C_6)-alkylsulfonyl-, (C_1-C_6)-alkylaminosulfonyl-, (C_5-C_{14})-arylaminosulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylaminosulfonyl-, (C_5-C_{14})-arylsulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylsulfonyl-, (C_5-C_{14})-aryl and (C_5-C_{14})-heteroaryl;

R^2 is $-C(O)R^5$;

R^3 is (A) (C_1-C_6)-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, fluorine, chlorine, bromine, cyano, trifluoromethyl, hydroxy or (C_1-C_6)-alkoxy, where all ~~residues~~ R^3 are independent of one another ~~and can be identical or different;~~

R^4 is hydrogen or (C_1-C_6)-alkyl;

R^5 is hydroxy or (C_1-C_8)-alkoxy;

R^6 and $R^{6'}$ are (A) hydrogen, (C_1-C_6)-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl where in the aryl residue one, two or three ring carbon atoms can be replaced by heteroatoms selected from the ~~series~~ group consisting of nitrogen, oxygen and sulfur, and ~~or~~ (C_5-C_{14})-aryl-(C_1-C_8)-alkyl- where in the aryl ~~moiety~~ of the aryl-alkyl- ~~residue~~

G is N or CH;

X is hydrogen;

Y is hydrogen;

Z is N;

R^1 is (A) (C_1-C_{18})-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl, (C_5-C_{14})-aryl-(C_1-C_8)-alkyl-, (C_5-C_{14})-heteroaryl and (C_5-C_{14})-heteroaryl-(C_1-C_8)-alkyl- where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by ~~identical or different substituents from the series~~ at least one member of the group consisting of fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, hydroxycarbonyl-, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl-, (C_1-C_6)-alkoxycarbonyl-, (C_1-C_6)-alkylcarbonyl-, (C_1-C_6)-alkylaminocarbonyl-, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy-, (C_5-C_{14})-arylcarbonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylcarbonyl-, (C_1-C_6)-alkanoylamino-, (C_5-C_{14})-arylsulfonylamino-, (C_1-C_6)-alkylsulfonylamino-, (C_1-C_6)-alkylamino-, di-$((C_1-C_6)$-alkyl)amino-, (C_1-C_6)-alkylsulfonyl-, (C_1-C_6)-alkylaminosulfonyl-, (C_5-C_{14})-arylaminosulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylaminosulfonyl-, (C_5-C_{14})-arylsulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylsulfonyl-, (C_5-C_{14})-aryl and (C_5-C_{14})-heteroaryl;

R^2 is $-C(O)R^5$;

R^3 is (A) (C_1-C_6)-alkyl, fluorine, chlorine, bromine, cyano, hydroxy and (C_1-C_6)-alkoxy, where all ~~residues~~ R^3 are independent of one another ~~and can be identical or different~~;

R^4 is hydrogen or (C_1-C_4)-alkyl;

R^5 is hydroxy or (C_1-C_6)-alkoxy;

Z is N;

R^1 is (C_1-C_{18})-alkyl, (C_3-C_{14})-cycloalkyl, (C_3-C_{14})-cycloalkyl-(C_1-C_8)-alkyl-, (C_5-C_{14})-aryl, (C_5-C_{14})-aryl-(C_1-C_8)-alkyl-, (C_5-C_{14})-heteroaryl ~~or~~ and (C_5-C_{14})-heteroaryl-(C_1-C_8)-alkyl- where aryl, heteroaryl, cycloalkyl and alkyl can be substituted one, two or three times by ~~identical or different substituents from the series~~ at least one member of the group consisting of fluorine, chlorine, bromine, cyano, trifluoromethyl, nitro, hydroxycarbonyl-, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkyl-, (C_1-C_6)-alkoxycarbonyl-, (C_1-C_6)-alkylcarbonyl-, (C_1-C_6)-alkylaminocarbonyl-, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy-, (C_5-C_{14})-arylcarbonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylcarbonyl-, (C_1-C_6)-alkanoylamino-, (C_5-C_{14})-arylsulfonylamino-, (C_1-C_6)-alkylsulfonylamino-, (C_1-C_6)-alkylamino-, di-$((C_1-C_6)$-alkyl)amino-, (C_1-C_6)-alkylsulfonyl-, (C_1-C_6)-alkylaminosulfonyl-, (C_5-C_{14})-arylaminosulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylaminosulfonyl-, (C_5-C_{14})-arylsulfonyl-, (C_5-C_{14})-aryl-(C_1-C_8)-alkylsulfonyl-, (C_5-C_{14})-aryl and (C_5-C_{14})-heteroaryl;

R^2 is $-C(O)R^5$;

R^4 is hydrogen or (C_1-C_4)-alkyl;

R^5 is hydroxy or (C_1-C_6)-alkoxy;

R^6 is hydrogen or (C_1-C_4)-alkyl;

s is zero;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their non-toxic physiologically tolerable salts ~~and their prodrugs~~.

5. A compound of ~~the formula I as claimed in one or more of~~ claims 1 ~~to 4~~, wherein D is -C(O)-NH-, ~~where this divalent residue is~~ bonded to ~~the group~~ E via its nitrogen atom;

retinopathies, psoriasis or rheumatoid arthritis.